Mastopathia Cystica and Mammary Carcinoma

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(Received for publication February 16, 1942)

The relationship of cystic disease of the breast, mastopathia cystica, to carcinoma is, and has always been, a subject of controversy. In 1906, when Bloodgood (2) considered severe parenchymatous hypertrophy, he and many other authors thought that this condition was a precancerous lesion and that the probability of cancer being associated with it was as high as 50 per cent. However, in 1921 (3) he described a group of 350 patients with chronic cystic mastitis, in 222 of whom he had had the opportunity to study the entire breast. In not a single instance did he find gross or microscopic cancer. In 1932 (4), a check-up examination on these patients showed that none had developed evidence of malignancy. At this time he added 30 new operative cases and almost 200 examples of unoperated "shotty" breast which had been followed by yearly examination. He reaffirmed the opinion formulated 10 years previously that the development of cancer of the breast after removal of a zone of the breast, which is the seat of chronic cystic mastitis, is apparently no more frequent than in the same number of women at the same age upon whom operation has not been performed (3).

Deaver and McFarland (10), after examining 335 cancerous breasts, found 23 in which abnormal resolution and carcinoma coexisted, but stated that they "cannot see the necessity for supposing that two conditions that happen to coexist must be connected to one another in the relation of cause and effect."

Kilgore (17) found carcinoma in only 1 of 19 instances of hyperplastic cystic disease showing clinically as a lump in the breast. Klingenstein (18) presented the follow-up data on 54 of an original group of 73 patients who had had partial excision of a breast for chronic cystic mastitis. Only 2 patients (3.7 per cent) were known to have developed carcinoma. Campbell (5) reported 43 examples of hyperplastic cystic disease among 233 cases of cystic disease of the breast of all types, which had been treated by local excision. In only one did carcinoma of the breast subsequently develop and then in an area far removed from the site of the previous operation. Of 57 patients treated by amputation of one breast, carcinoma developed in the remaining breast of but one. Thus, of 290 patients followed, only 2 or 0.7 per cent developed carcinoma. Johnson (15) followed 61 of 101 patients with cyst of the breast for periods of 1 to 20 years and found no evidence of carcinoma. In 4 instances in which both a cyst and carcinoma were dealt with, the carcinoma was on the same side as the cyst in 2 and on the opposite side in 2.

Lewis and Geschickter (19) also emphasized Bloodgood's views. They reported 3 deaths from carcinoma among 271 patients with adenosis of the breast who had been followed for more than 5 years, and 1 death from carcinoma among 252 patients with cystic disease followed for the same period. In a study of 2,075 carcinomas of the breast, only 0.5 per cent of the usual types were found to show changes characteristic of Schimmelbusch's disease, yet 30 per cent having carcinoma of the ductal (comedo) type were associated with breast tissue showing these changes. Greenough and Simmons (14) traced 83 women with partial resection of the breast for cystic disease over periods of 1 to 17 years (average 7 years). In 4 (4.8 per cent) carcinoma developed in the remaining breast tissue. Fischer (13) found cystic disease in 14 per cent of 151 patients. Rodman (22) found that chronic cystic mastitis was associated with carcinoma in 15.5 per cent of more than a hundred cases studied by him. Cheattle and Cutler (7, 8) stated that at least 20 per cent of all carcinomas of the breast can be traced directly to mastopathia cystica. This figure is in close agreement with that of Semb (23), who found the incidence of carcinoma in 100 cases of "fibro-adenomatosis cystica" to be 24 per cent, and of Morpurgo (27), who found cystic changes in 24 per cent of 196 patients with carcinoma of the breast. Dietrich and Frangenheim (11) studied 500 mammary gland preparations of which 233 (46.6 per cent) showed mastopathia cystica. Sixty-eight of the 233 (29.4 per cent) showed coexistent carcinoma.

Ewing (12) found minimal carcinomas in 50 per cent of the breasts excised for cystic disease. Dahl-Iverson and Starup (6) found coincidence of carcinoma and mastopathia cystica in 44 per cent of 34 cases studied by them. Keynes (16) reported on 116 specimens of breast tissue removed post-mortem, of which 57 were normal and 59 showed "inflammatory lesions." He also reported that in 25 examples of carcinoma of the breast, 20 (80 per cent) showed some evidence of "chronic mastitis." Upon histologic study, Charteris (6) found that 41 (85 per cent) of 48 breasts removed for carcinoma were also the seat of chronic cystic mastitis in some degree. The malignant growth was believed to have arisen from the ducts in 31 of the 48 (64 per cent). MacCarty and Mensing (20) examined 907 breasts removed for carcinoma and found evidence of mastopathia cystica in 100 per cent of them.

Thus, it can be seen that a historical review of the literature from either a clinical or pathologic viewpoint will reveal considerable evidence to support either the casual or the causal relationship of mastopathia cystica and carcinoma. The most recent report is that of Warren (24), who followed clinically for at least 5 years a group of women who had portions of the breast removed. He compared the incidence of carcinoma in this group with that of the general female population and found that 35 cancers occurred in 1,044 individuals with chronic mastitis and chronic cystic mastitis. On contrasting specific cancer rates with those of the female population of Massachussets, evidence was found that the cancer rate for women with pre-existing breast lesions is 4.5 times as great as for all women, and that this predominance is especially marked in the decades below 50 years of age.

The definition of mastopathia cystica depends, to a large degree, upon each author's opinion as to the nature of the disease. Cheattle and Cutler (7) considered that mastopathia cystica includes two distinct diseases. The first, named "mazoplasmia," is a physiologic rather than a pathologic process, and there are no other lesions in the breast such as fibroadenomas, cysts, or papillomas. It is characterized by desquamation of the epithelial cells in the terminal ducts and acini, accompanied by hyperplasia of the periacinarial and periacinar connective tissue. The second type of epithelial hyperplasia results in the formation of cysts, minute to large, and is designated "cystipherous desquamative epithelial hyperplasia." It was the opinion
of these authors that this type of hyperplasia terminates in neoplasia in at least 20 per cent of the cases.

Whitehouse (25) pointed out that in his investigations he never saw cystipherous hyperplasia in a breast which did not, in some part, show also mastoplasia. He felt that mastoplasia was apparently the natural result of excessive stimulation of the mammary epithelium by the luteal hormone, and that repeated cyclical stimulation of the mammary epithelium results in the production of excessive secretion and cystic disease. He suggested the term "mastopathia" to designate that stagnation of the mammary gland which results from the lack of physiologic monthly drainage of that organ.

Willer (26) and Berning and Bucker (1) considered the apocrine glands very important in the formation of benign and malignant neoplasms. Willer found that apocrine glands are rare in the normal breast, except in the periphery, but that they occur with great regularity in mastopathia cystica. Berning and Bucker made the diagnosis of mastopathia cystica upon the presence of pale-celled epithelium with eosinophilic granules. The name "pale epithelium" is derived from the fact that in such epithelial cells the nucleus is very small in comparison to the size of the cell and lies in its basal part. They also described epithelial proliferation with formation of true and pseudo-growths but without division figures or infiltration.

THE MORPHOLOGIC COMPLEX OF MASTOPATHIA CYSTICA

Our concept of the morphology of mastopathia cystica includes the presence of dilated ducts accompanied by diffuse fibrosis. The alveolar ducts are most commonly involved, although the main lactiferous ducts, the terminal ducts, and even acini may show dilatation. Numerous ducts or only one may be involved. The cells lining the ducts vary greatly in character. They may be cuboidal or columnar, and are often flattened. The cytoplasm is pale-staining and slightly basophilic with hematoxylin and eosin. The nuclei are deep-staining and round or oval. In many ducts the cells are greatly increased in number as well as in size, and coalesce to form projections, arches, or even solid sheets which may partially or completely fill the lumen. Papillary ingrowths into dilated ducts may be so atypical that only the absence of infiltrative growth indicates the benign nature of the process. These ingrowths were found in 68 per cent of our cases.

Acini as well as ducts are frequently involved. When distended, the epithelium of the acini is very low, appearing to be atrophic. Large retention cysts may be formed which may coalesce to form composite cysts.

There is an increase in the periductal and periacinar connective tissue, resulting in a diffuse fibrosis of the breast and causing wide separation of the lobules. The connective tissue may undergo hyaline degeneration when the fibrosis is of long standing and pressure atrophy of glandular tissue may result. The fibrosis may be associated with lymphocytic and/or plasma cell infiltration of the stroma, which may be localized in the region of the dilated ducts or may be diffusely scattered throughout the involved breast.

Hypertrophic pale-celled glandular epithelium, of the apocrine gland type, was found lining small glands and cysts of various sizes in approximately 60 per cent of our cases. In such areas the cuboidal or cylindrical cells are filled with closely packed eosinophilic granules or with a homogeneous eosinophilic cytoplasm. A small, round, poorly stained nucleus is located at the base of the cell. This epithelium is frequently thrown into folds and forms arches in the lumen. Around the base of the epithelium the layer of myoepithelium is thin as compared to that around the more normal secretory glands.

Glandular hyperplasia of the terminal ducts and acini was present in 62 per cent of our cases. There may be considerable increase in the number of acini in each lobule. Frequently the glandular hyperplasia is definitely atypical and the acini are filled with nests of cells. The periductal and periacinar fibrosis is particularly prominent in these areas. The abnormal response of the breast to excessive cyclical stimulation is evidenced by the dilatation of the terminal ducts and particularly of the acini. This is seen in scattered portions of the breast with normal breast tissue in the intervening portions, and also in breasts showing other cystic changes. The epithelial cells become swollen and tall, and there may be desquamated cells in the lumen of the ducts. There is also a definite periductal fibrosis with a localized lymphocytic infiltration.

STATISTICAL ANALYSIS

The material for this study was obtained from 330 women with lesions of the breast which necessitated operative removal of a specimen for microscopic examination during the period from July 1, 1937, to June 30, 1939. During this period 48 additional examples of carcinoma of the breast were seen; but these were excluded from further consideration because they were either prepared slides submitted from other institutions or small "biopsy" specimens not suitable for the purposes of this study. The material suitable for study may be tabulated as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases</th>
</tr>
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<tbody>
<tr>
<td>With carcinoma</td>
<td>118</td>
</tr>
<tr>
<td>(All mastectomies; 4 to 15 blocks of tissue examined from each breast.)</td>
<td></td>
</tr>
<tr>
<td>Without carcinoma</td>
<td>212</td>
</tr>
<tr>
<td>(Partial mastectomies, a few complete mastectomies and numerous generous &quot;biopsy&quot; specimens; 2 to 10 blocks examined from each patient.)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous benign neoplasms, abscesses, and various other lesions</td>
<td>130</td>
</tr>
<tr>
<td>Total</td>
<td>330</td>
</tr>
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Definite evidence of coexisting mastopathia cystica was found in 67, or 56.7 per cent, of the 118 breasts removed for carcinoma, either in the immediate vicinity of the tumor or elsewhere in the breast. In 16 cases, 13.5 per cent, the carcinoma appeared to be arising in the area of mastopathia cystica. In these specimens the epithelial proliferation within the ducts was not only atypical but the basement membrane was frequently disrupted, and there was carcinomatous invasion of the surrounding tissues. Not only was there a close similarity between the infiltrating cells and the atypical papillary ingrowths within the dilated ducts, but also physical continuity between the two could be traced in frequent examples. In such there was ample evidence to justify the assumption that the carcinoma had arisen in the altered epithelium of mastopathia cystica. It will be recalled that in 68 per cent of the breasts with mastopathia cystica in this series, atypical papillary ingrowths into the dilated ducts were found. These were frequently associated with nests or solid sheets of cells completely filling the ducts. Only lack of evidence of infiltrative growth differentiated some of these areas from those known to be carcinomatous.

Since carcinoma of the breast and mastopathia cystica are both relatively common conditions, the possibility of their chance coincidence must be considered. Utilizing the basic information which follows, a fourfold table was arranged and the $X^2$ test was applied to the 330 specimens examined (ignoring the 48 cases of carcinoma seen in "biopsy" material only).

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastopathia cystica</td>
<td>67 (57 per cent) also showed mastopathia cystica.</td>
<td>51 (43 per cent) showed no mastopathia cystica.</td>
<td>118</td>
</tr>
<tr>
<td>Absent</td>
<td>51</td>
<td>130</td>
<td>181</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>212</td>
<td>330</td>
</tr>
</tbody>
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For the above data,

$$X^2 = \frac{(130)(167) - (51)(82))^2}{118(212)(149)(181)} = 10.029$$

This value for $X^2$ indicates that the chances of getting the above results, if mastopathia cystica and carcinoma are independent, are of the order of 1 in 1,000 ($27$). Inasmuch as the normal range of probability by this test is 1 to 5 in 100, it is obvious that the association of the two conditions is highly significant.

**SUMMARY**

In a series of 330 consecutive surgical specimens of breast tissue, mastopathia cystica was found in 67 of a total of 118 with carcinoma. Application of the $X^2$ test to the resulting data indicates that this degree of association cannot be expected through chance distribution and is statistically significant. On the basis of these findings, a causal relationship between mastopathia cystica and mammary carcinoma must be accepted. Although the highest incidence of mastopathia cystica is found in the decade of 40 to 50 years, the incidence of carcinoma of the breast continues at a high level for the next three decades. Any patient upon whom a diagnosis of mastopathia cystica is established should be followed carefully by repeated clinical examinations. If any change in the character of the lesion develops, histologic evidence of its nature should be considered essential.

I am indebted to Dr. Churchill Eisenhart of the University of Wisconsin, Madison, Wisconsin, for a critical evaluation of the statistical method.—Author.

**REFERENCES**

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